REMARKS

In view of the following remarks, the Examiner is requested to allow claims 32, 52, 62-69, 84, 85, 88, 89, 104-107 and 110-113, the only claims pending and under examination in this application.

Formal Matters

Claim 111 has been amended to specify that at least three proteins are removed. The remaining amendments to the claims are made for clarity and to make sure that, where appropriate, dependent claims terms have appropriate and clear antecedent basis, to correct typographical errors, and to correct errant dependencies. As no new matter has been added by way of these amendments, entry thereof by the Examiner is respectfully requested.

Withdrawn Rejections

The Examiner is acknowledged and thanked for the withdrawal of prior Rejections under 35 U.S.C. § 102(b) and (e) and under 35 U.S.C. § 103(a).

Claim Objections

The Examiner is thanked for pointing out that Claim 111 did not show the deleted word "three" and the added word "the." The cited typographical error has been corrected and the instant claim now reads as intended.

Claim Rejections – 35 U.S.C. § 112

Claims 32, 52, 62-69, 84, 85, 88, 89, 104-107 and 110-113 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In making the rejection, the Examiner alleges that in claims 63 and 84, the claim preambles do not correspond to the method outcomes. Specifically, the Examiner alleges that the methods appear complete upon performance of

"removing," while the last step of "recovering" appears extraneous. Without in any way agreeing with the position of the Office and solely to expedite prosecution of the application, the Applicants have amended claims 63 and 84 to further indicate the relationship of the preambles of the claims to their outcomes.

The remaining objections und 35 U.S.C. § 112, second paragraph have been addressed by amending the claims for clear antecedent basis.

In view of the foregoing discussion, it is believed that the rejection has been adequately addressed. Withdrawal of the rejection is respectfully requested.

Claim Rejections – 35 U.S.C. § 102

Claims 32, 52, 62-69, 84, 88, 89, 104, 105 and 110-1 13 are rejected under 35 U.S.C. 102(e) as allegedly being anticipated by Hutchens & Yip (hereinafter "Hutchens," US 6,225,047).

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

It is respectfully submitted that Hutchens fails to teach a method using an affinity binding composition including a first solid phase matrix with a first receptor immobilized thereon capable of specific binding to the first protein but not the second protein and a second solid phase matrix with a second receptor immobilized thereon capable of specific binding to the second protein but not the first protein, in which each solid phase matrix is a plurality of particles and the first and second solid phase matrices are present as a mixture in the binding composition. It is not seen where these elements are taught by Hutchens.

Specifically, the Applicants respectfully submit that the cited passages of Hutchens do not teach what the Examiner alleges.

The Examiner defines the mixture of a plurality of solid phase matrices with a plurality of receptor types as allegedly found in Hutchens as:

> i. a plurality of receptor types (see *e.g.*, col. 20, line 8, "adsorbent") having different protein binding specificities relative to each other (see *e.g.*, col. 21, line 36, "Incremental or Gradient Adsorbent Surfaces"; see also, col. 13, lines 52-53, "multiplex adsorbent"), each receptor type immobilized on separate particles (see col. 20, lines 9-10, "polymeric or glass bead"), the particles present as a mixture in said affinity binding composition [Office Action, pages 4-5].

The Applicants respectfully point out that the cited passages in Hutchens nowhere teach a first solid phase matrix with a first receptor immobilized thereon capable of specific binding to the first protein but not the second protein and a second solid phase matrix with a second receptor immobilized thereon capable of specific binding to the second protein but not the first protein, in which each solid phase matrix is a plurality of particles and the first and second solid phase matrices are present as a mixture. The first relevant passage of Hutchens (column 13, lines 47-62) is reproduced below for convenience:

> "Adsorbent" refers to any material capable of adsorbing an analyte. The term "adsorbent" is used herein to refer both to a single material ("monoplex adsorbent") (e.g., a compound or functional group) to which the analyte is exposed, and to a plurality of different materials ("multiplex adsorbent") to which a sample is exposed. The adsorbent materials in a multiplex adsorbent are referred to as "adsorbent species." For example, an addressable location on a substrate can comprise a multiplex adsorbent characterized by many different adsorbent species (e.g., anion exchange materials, metal chelators, or antibodies), having different binding characteristics.
>
> "Adsorb" refers to the detectable binding between an absorbent and an analyte either before or after washing with an eluant (selectivity threshold modifier).

In light of the above passage from Hutchens, one of ordinary skill in the art understands that an addressable location on a substrate bearing an adsorbent as

PAGE 12/23 * RCVD AT 10/10/2007 5:09:34 PM [Eastern Daylight Time] * SVR:USPTO-EFXRF-5/2 * DNIS:2738300 * CSID:6503273231 * DURATION (mm-ss):03-54

described by Hutchens – whether monoplex or multiplex – binds to "the analyte," or "an analyte," i.e., a single molecule.

As such, Hutchens at best fails to teach a first solid phase matrix with a first receptor immobilized thereon capable of specific binding to the first protein but not the second protein and a second solid phase matrix with a second receptor immobilized thereon capable of specific binding to the second protein but not the first protein, where the matrices are present as a mixture, as is claimed.

The Applicants further respectfully point out that the passage in Hutchens, column 36, lines 52-67, cited by the Examiner as allegedly describing removal of undesired analytes until a desired analyte remains in the sample, specifically teaches that the cited particles ("adsorbents") present in different binding conditions are not present as a mixture. The relevant passage of Hutchens at column 36, lines 28-62 is reproduced below for convenience:

A. Methods For Sequentially Extracting Analytes From A Sample

Retentate chromatography involves the analysis of retention of an analyte under a plurality of adsorbent/eluent conditions. One variation of this method is sequential extraction. In sequential extraction a sample is not independently exposed to two different selectivity conditions. Rather, the sample is exposed to a first selectivity condition to extract certain analytes from the sample onto the adsorbent, and leave non-adsorbed analytes in the eluent. Then, the eluent is exposed to a second selectivity condition. This further extracts various analytes from the eluant. Frequently, if the adsorbents in the first and second exposure have different basis for attraction (e.g., normal phase and hydrophobic) the adsorbent will extract a different set of analytes from the eluent. This second eluant is then exposed to a third selectivity condition, and so on. In one method of practicing sequential extraction, the adsorbent is placed at the bottom of a well so that sample can be mixed on top of it. An eluant is added to the adsorbent and after allowing binding between analytes in the sample, the eluant wash is collected. The collected wash is then exposed to a second adsorbent, and analytes are extracted from the sample by binding.

In one embodiment, the goal of sequential extraction is preparative rather than analytical. More specifically, the goal may be to extract all but a desired analyte from the sample. In this case, the sample is usually small, e.g., a few microliters on a spot about a few millimeters in diameter. The adsorbents are selected so as not to adsorb an analyte one wishes not to be depleted from the sample. After several iterations the finally collected wash is depleted of un-desired analytes, leaving the desired ones for subsequent analysis by, for example, desorption spectrometry or traditional chromatographic methods.

In another embodiment, unretained sample is, itself, analyzed for analytes by any analytic technique. Even after a single retention step, this process allows one to examine materials adsorbed to an adsorbent and those analytes that are not adsorbed.

In light of the above passage from Hutchens, one of ordinary skill in the art understands that to perform preparative extraction to remove undesired analytes leaving a desired analyte remaining in a sample, extractions for each undesired analyte are performed sequentially so that each extraction exposes an analyte to one selectivity condition at a time ("a first selectivity condition," "a second selectivity condition"). Hutchens teaches that each extraction is performed in sequence upon the eluant from each successive extraction/wash step.

As such, this passage of Hutchens also fails to teach a first solid phase matrix with a first receptor immobilized thereon capable of specific binding to the first protein but not the second protein and a second solid phase matrix with a second receptor immobilized thereon capable of specific binding to the second protein but not the first protein, where the matrices are present as a mixture, as is claimed.

Accordingly:

i. where Hutchens allegedly teaches mixed adsorbents ("multiplex adsorbent"), Hutchens makes clear that all such adsorbents are capable of binding to the same analyte (column 13, lines 47-62); and

ii. where Hutchens allegedly teaches the removal of multiple proteins by using multiple selectivity conditions, Hutchens makes clear that such conditions are used in series, as different extractions each upon the eluant from the preceding extraction (column 36, lines 28-62).

As such, Hutchens at least fails to teach a first solid phase matrix with a first receptor immobilized thereon capable of specific binding to the first protein but not the second protein and a second solid phase matrix with a second receptor immobilized thereon capable of specific binding to the second protein but not the first protein, in which each solid phase matrix is a plurality of particles and the first and second solid phase matrices are present as a mixture, as is claimed. Accordingly, Hutchens fails to teach each and every limitation of the instant claims.

In view of the foregoing discussion, it is believed that the rejection has been adequately addressed. Withdrawal of the rejection is respectfully requested.

Claims 62-64, 66, 84-85, 88-89, 104 and 110-113 are rejected under 35 U.S.C. 102(b) as being anticipated by Rubenstein (US 5,879,881).

The Applicants respectfully submit that Rubenstein fails to teach a method including a first solid phase matrix with a first receptor immobilized thereon capable of specific binding to the first protein but not the second protein and a second solid phase matrix with a second receptor immobilized thereon capable of specific binding to the second protein but not the first protein wherein each solid phase matrix is a plurality of particles and the first and second solid phase matrices are present as a mixture in the binding composition, such that when the sample is contacted with the affinity binding composition, the first protein present in the sample binds to the first

receptor present on the first solid phase matrix such that the first protein is removed from the sample and the second protein present in the sample binds to the second receptor present on the second solid phase matrix such that the second protein is removed from the sample and the modified sample is thereby produced, in which the modified sample is not bound by a solid phase matrix; and recovering the modified sample. It is not seen where these elements are taught by Rubenstein.

The Applicants submit that the cited passages of Rubenstein do not teach what the Examiner alleges.

The Examiner defines the plurality of particles present as a mixture as allegedly found in Rubenstein as:

> i. a plurality of receptor types having different protein binding specificities relative to each other (see, e.g., col. 6, line 5, "different enzyme labeled antibodies"; see also, line 20, "panel of allergens"; see also, lines 35-36, "different receptor"), each receptor type immobilized on separate particles (see *e.g.*, col. 6, line 7, "groups of microspheres"; see also, lines 15-16, "distinct groups of microspheres"; see also, line 34, "groups of microspheres"), the particles present as a mixture in said affinity binding composition

The Examiner defines the removing proteins from a sample as allegedly found in Rubenstein as:

> removing (see e.g., col. 6, line 20, "capturing"; see also, line 35, "the capture") at least a first protein and a second protein (see e.g., col. 6, line 1, "at least two selected analytes"; see also, lines 20-21, "IgE antibodies"; see also, lines'35-36, "different ligands") from a sample, said removing step comprising: contacting the sample with an affinity binding composition (see e.g., col. 6, line 8, "porous matrix"; see also, line 19, "matrix"; see also, Fig. 4, matrix 10) [Office Action, page 5].

The Examiner defines the step of recovering as allegedly found in Rubenstein as:

> (2) recovering the modified sample (see Fig. 6, "second absorbent member 38") (Office Action, page 6).

The Applicants respectfully point out that Rubenstein nowhere teaches a first solid phase matrix with a first receptor immobilized thereon capable of specific binding to the first protein but not the second protein and a second solid phase matrix with a second receptor immobilized thereon capable of specific binding to the second protein but not the first protein, where each solid phase matrix is a plurality of particles and the first and second solid phase matrices are present as a mixture in the binding composition. Indeed, Rubenstein teaches the opposite. The relevant passage of Rubenstein at column 5, lines 44-65, is reproduced below for convenience:

> A preferred solid phase system of the present invention comprises plural groups of microspheres entrapped in discrete zones, preferably in a predetermined pattern, within the matrix. Each group of microspheres is bound, prior to entrapment, with a different receptor, such as an antibody or antigen capable of capturing a different ligand of interest. Accordingly, in one embodiment of the invention, each group of microspheres comprises a population of microspheres bound with the same antibody, antigen or other receptor selected for use in the assay. Alternatively, a group of microspheres may comprise a mixture of microspheres to which are bound different receptors. For example, in the case of an immunoassay for an antigen, each group of microspheres may comprise at least two subpopulations of microspheres wherein each subpopulation is bound with an antibody, preferably a monoclonal antibody, capable of binding with a different determinant or epitope of the antigen. Preferably, the monoclonal antibodies bound with the subpopulations of microspheres comprising a distinct group of microspheres are selected to have a specific reactivity with non-interfering epitopes of the target ligand, thereby enhancing the sensitivity and specificity of the assay.

In light of the above passage from Rubenstein, one of ordinary skill in the art understands that each group of microspheres in a discrete zone, whether bearing a single receptor or multiple receptors, binds to "the target ligand," e.g., "the antigen," i.e., a single molecule.

As such, Rubenstein at best fails to teach a first solid phase matrix with a first receptor immobilized thereon capable of specific binding to the first protein but not the second protein and a second solid phase matrix with a second receptor immobilized thereon capable of specific binding to the second protein but not the first protein, where each solid phase matrix is a plurality of particles and the first and

second solid phase matrices are present as a mixture in the binding composition, as is claimed. Instead, Rubenstein teaches throughout the reference that microspheres with binding specificities for different proteins are present in different zones, and not as a mixture.

The Applicants further respectfully point out that, throughout the disclosure of Rubenstein, the alleged proteins being removed from a sample ("at least two selected analytes"; see also, lines 20-21, "IgE antibodies"; see also, lines'35-36, "different ligands") are recovered by attachment to the sold phase matrix(see e.g., col. 6, line 20, "capturing"; see also, line 35, "the capture") at least a first protein and a second protein (see e.g., col. 6, line 1, "at least two selected analytes"; see also, lines 20-21, "IgE antibodies"; see also, lines'35-36, "different ligands").

As such, the cited proteins are not absorbed by the cited second absorbent member (see Fig. 6, "second absorbent member 38"), consistent with the fact that Rubenstein is directed to a positive, not negative, selection method. Specifically, the "sample" which Rubenstein instructs be recovered throughout the disclosure is what is conjugated to the beads.

As such, Rubenstein nowhere teaches that the contents of the cited second absorbent member (see Fig. 6, "second absorbent member 38") are recovered. Instead, upon reading Rubenstein, one of ordinary skill in the art understands that the cited second absorbent member is present, first, to draw fluid through the filter containing the beads which trap the sample (please see, by way of example, Column 7, lines 15-37, wherein the function of the second member is explained), and second, as a waste trap (please see column 8, lines 18-59, describing the use of the device, in which several fluids are added to the apparatus in series, including analyte containing, receptor conjugate, enzymatic detection fluid and wash fluids, all of which are drawn into the cited second absorbent member; see also Examples I and II at columns 9 and 10, both substantiating this understanding of the function of the cited second absorbent member). It is nowhere taught by Rubenstein that the contents of the cited second absorbent member are recovered.

Accordingly, Rubenstein further fails to teach a method such that when the sample is contacted with the affinity binding composition the proteins are removed from the sample and the modified sample is thereby produced, in which the modified sample is not bound by a solid phase matrix; and recovering the modified sample, as is claimed.

In view of the foregoing discussion, it is believed that the rejection has been adequately addressed. Withdrawal of the rejection is respectfully requested.

Claim Rejections – 35 U.S.C. § 103

Claims 62-64, 66, 84-85, 88-89, 104-107 and 110-113 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ullman *et al.* (hereinafter "Ullman," US 5,137,808) in view of Rubenstein (US 5,879,881).

In order to meet its burden in establishing a rejection under 35 U.S.C. § 103 the Office must first demonstrate that the combined prior art references teach or suggest all the claimed limitations. See Pharmastem Therapeutics v. Viacell et al., 2007 U.S. App. LEXIS 16245 (Fed. Cir. 2007) ("the burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make [every element of] the composition or device, or carry out the [entire] claimed process, and would have had a reasonable expectation of success in doing so," (citing KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1740 (2007))); and see Omegaflex, Inc. v. Parker-Hannifin Corp., 2007 U.S. App. LEXIS 14308 (Fed. Cir. 2007) ("[t]he Supreme Court recently explained that 'a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art,'" (citing KSR Int'l Co. at 1741)); and see Dystar Textilfarben GmbH v. C.H. Patrick Co., 464 F.3d 1356, 1360 (Fed. Cir. 2006) ("[once] all claim limitations are found in a number of prior art references, the factfinder must determine '[w]hat the prior art teaches, whether it teaches away from the claimed invention, and whether it motivates a combination of teachings from different references,'" (citing In re Fulton, 391 F.3d 1195, 1199-1200 (Fed. Cir. 2004))).

In making this rejection, the Examiner alleges that Ullman teaches all the elements of the claims with the exception of a plurality of receptor types having different protein binding specificities relative to each other, each receptor type immobilized on separate particles, the particles present as a mixture in the affinity binding composition, for which elements the Examiner turns to Rubenstein. The Applicants submit that the references, individually and in combination, fail to teach or suggest what is alleged by the Examiner.

First, the Applicants respectfully submit that the cited failure by Ullman to teach a plurality of receptor types present as a mixture does not exhaust the deficiencies of Ullman. Specifically, Ullman additionally fails to teach the step of recovering the sample, both modified and unmodified.

The Examiner defines the method for producing a modified sample as allegedly found in Ullman as:

> (1) removing (see Abstract, "capturing") at least a first protein and a second protein (see col. 20, lines 32-44) from a sample, said removing step comprising: contacting the sample with an affinity binding composition (see Fig. 1A, "immunosorbing zone 84");
>
> (2) recovering the modified sample (see Fig. 1A, "absorbent means 20"; see col. 16, lines 29-32).

The Applicants respectfully point out that, throughout the disclosure of Ullman, the proteins being detected (see col. 20, lines 32-44) are non-diffusively immobilized by attachment to the an affinity binding composition (see Fig. 1A, "immunosorbing zone 84") . They are absorbed by the cited absorbent means (see Fig. 1A, "absorbent means 20"; see col. 16, lines 29-32), consistent with the fact that Ullman is directed to detecting the contents of the apparatus within the strip of bibulous material, but not removing any content from it (note especially that all absorptive materials described are "non-removably confined," in the housing, throughout the

reference). Specifically, in all descriptions of the use of the invention by Ullman, no introduced sample is at any point recovered or made recoverable from the apparatus. This is consistent with the fact that Ullman is directed to a diagnostic, not preparative, device which is not designed to provide a means to recover samples.

As such, Ullman nowhere teaches that the contents of the cited absorbent means (see Fig. 1A, "absorbent means 20"; see col. 16, lines 29-32) are recovered. Instead, upon reading Ullman, one of ordinary skill in the art understands that the cited absorbent means is present, first, to draw fluid through the immunosorbing zone which retains the sample and second, incidentally, as a waste trap (please see, by way of example, column 10, lines 36-53, wherein the function of the absorbent means is explained, specifically, as a pump to pump liquid through and out of the immunosorbing zone; column 12, lines 47-54, wherein liquid absorbing member 20 is confined in a recessed area; Figures 1-6, wherein the absorbing member is in all cases placed in such a way as to be inaccessible).

Further, exemplary applications of the apparatus of Ullman (please see column 18, line 28 through column 21) all support this understanding of the diagnostic function of the apparatus and the use of cited absorbent means 20 as a waste trap. Fluids including analyte-containing, label-containing, and wash fluids are all drawn through strip 18 into the absorbent means 20 (see Figure 1A). The presence of analytes in the strip connecting the immunosorbing zone and the absorbent means are then detected. It is nowhere taught by Ullman that any contents of the absorbent material are at any point to be recovered from the absorbent means.

Accordingly, since Ullman is directed to an analytic method in which all material introduced to the apparatus is retained therein, Ullman fails to teach, or even to suggest, a method such that when the sample is contacted with the affinity binding composition the proteins are removed from the sample and the modified sample is thereby produced, in which the modified sample is not bound by a solid phase matrix; and recovering the modified sample, as is claimed.

The Applicants further submit that, as discussed above, Rubenstein fails to teach a first solid phase matrix with a first receptor immobilized thereon capable of specific binding to the first protein but not the second protein and a second solid phase matrix with a second receptor immobilized thereon capable of specific binding to the second protein but not the first protein, in which each solid phase matrix is a plurality of particles and the first and second solid phase matrices are present as a mixture. Since Rubenstein was cited for precisely these elements, Rubenstein fails to remedy the several deficiencies of Ullman.

The rejection may be withdrawn for this reason alone.

Further, since Rubenstein makes clear to one of ordinary skill in the art that the flowthrough from the device of Rubenstein enters a waste trap from which no effluent material is recovered, Rubenstein fails to teach, or even to suggest, a method such that when the sample is contacted with the affinity binding composition the proteins are removed from the sample and the modified sample is thereby produced, in which the modified sample is not bound by a solid phase matrix; and recovering the modified sample.

As such, since neither reference teaches or suggests recovery of the modified sample not bound by a solid phase matrix; and further, since Rubenstein fails to teach adsorbent species present as a mixture with receptors that have at least one mutual exclusivity with respect to a first and second protein, a *prima facie* case of obviousness is not made and the rejection may be withdrawn.

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CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone Bret Field at (650) 327-3400.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-1078, order number 10030634-2.

Respectfully submitted,

Date: October 10, 2007

By: _____
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